

A COMPARATIVE STUDY OF TOCOLYSIS WITH ATOSIBAN VS PROGESTERONE IN MANAGEMENT OF PRETERM LABOR

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ABSTRACT

OBJECTIVE

A cross sectional prospective study in Bint Al-Huda Teaching Hospital extended from 1st of October 2017 to 15th of February 2018.

The study was undertaken with the aims of determining the efficacy of atosiban in management of preterm labor and comparison atosiban with progesterone in prolongation of pregnancy and postpone preterm labor.

MATERIALS & METHODS

In the study 130 pregnant women presenting with threatened preterm labor between 24 – 34 wks of gestation, who were assigned to receive tocolysis with either atosiban (n= 65) or progesterone (n= 65)

RESULTS

The effectiveness of tocolysis was determined by the duration of pregnancy prolongation for more than 48 hrs, 7 days or 14 days. The primary outcome was the rate of pregnancy prolongation for 48 hrs.

Tocolysis failed in 8 women in atosiban group while failed in 20 women in progesterone group, 12 women delivered after 48 hrs in atosiban group while 23 women in progesterone group, 20 women delivered after 7 days in atosiban group while 12 women in progesterone group, 25 women delivered after 14 days in atosiban group while 10 women in progesterone group . So there was a significant association between the treatment strategies in form of atosiban or progesterone with outcome of delivery, where P value < 0.05.

CONCLUSIONS

The atosiban more effective than progesterone in prolongation of pregnancy in threatening preterm labor .

KEY WORDS: Preterm Labor, Tocolysis, Atosiban & Progesterone

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INTRODUCTION

Preterm birth is defined as delivery before 37 wks completed of gestation, preterm is responsible for approximately 75% of all neonatal death & 50 % of childhood neurological morbidities ⁽¹⁾, also suffer serious morbidity such as bronchopulmonary dysplasia & visual abnormalities ^(1,2).

Preterm birth is also associated with both high immediate & long term costs after discharge from hospital (2). Infants born at less than 28 wks spend more time as long in hospital as full term babies in the first 5 yrs of life (3). Therefore postponing delivery for 48 hrs in order to allow maximal effect of maternal parenteral steroid administration & referring the mother to centre with neonatal intensive care unit. Facilities are with threatening preterm delivery, however tocolytic drugs used for inhibition of acute preterm labor have not been shown to be very effective (4).

Atosiban is an inhibitor of the hormone oxytocin & vasopressin, it's used as an intravenous medication as a labor repressant (tocolytic) to halt premature labor, it was developed by Ferring pharmaceuticals in Sweden & first reported in the literature in 1985 (5).

Atosiban is a synthetic peptide oxytocin antagonist on the myometrium & prevents oxytocin stimulated increases in inositol triphosphate production (6), this ultimately prevent the release of stored calcium from the sarcoplasmic reticulum & subsequent opening of voltage gated calcium channels(8).

Common side effect of atosiban are 10% gastrointestinal (nausea & vomiting), dizziness, headache & hyperglycemia (9), no direct physiological effects or abnormal fetal movement were observed during the management of preterm labor.

Progesterone employs biological effects in the myometrium & uterine cervix, progesterone withdrawal or decline in its action in animal studies has been proposed as a key control mechanism for cervical ripening by several researchers (10).

Although the exact mechanism of action of progesterone in preventing preterm labor is still unknown, there are two widely accepted mechanisms. A local anti-inflammatory effect at the maternal – fetal interface that counteracts the inflammation sequence leading to preterm labor, & its ability to modulate other biological processes implicated in cervical ripening (11). We used intramuscular of 17 – alphahydroxy progesterone caproate weekly with 200 mg vaginal progesterone suppositories daily & follow up the progress of preterm labor (12).

METHODOLOGY

The study comprised 130 pregnant women presented with preterm labor between 24 – 34 wks of gestation. The inclusion criteria were a satisfactory condition of the pregnant women & fetus, singleton pregnancy, un ruptured membranes, gestational age between 24-34 wks with registered uterine contractions (4 or more contractions 30 minutes apart & lasting 30-60 seconds).

Cervical dilation of 1-3 cm & 50% cervical shortening from the base line values, exclusion criteria were serious health conditions of the pregnant woman requiring emergency delivery including (sever preeclampsia, eclampsia, placenta previa & placental abruption, fetal distress, chorioamnionitis, congenital fetal defects, acute fetal death, multiple gestations or history of cardiovascular disease).

The results of this meta – analysis are based for a large part on one randomized controlled trial comparing atosiban& progesterone in the management of preterm labor for more than 24 hrs for reduction of neonatal respiratory distress syndrome.

Tocolytic therapy was initiated immediately after the diagnosis, determining gestational age, assessing fetal & maternal health.

Tocolysis with atosiban & progesterone was administered in 65 atosiban & 65 progesterone respectively.

The atosibantocolysis dosage regime: initial administration dose 6.5 mg bolus by slow injection over 1 minute immediately followed by continuous infusion of 300 mg \minute for 3 hrs then decrease infusion rate to 100 mg \minute for up to 45 hrs, maximum total dose \ duration 330.75 mg \ 48 hrs while the progesterone tocolysis dosage regime : we used intramuscular of 17 – alphahydroxy – progesterone caproate weekly with 200 mg vaginal progesterone suppositories daily .

The effectiveness of tocolysis was determined by the duration of pregnancy prolongation (for 48 hrs, 7 days more than 14 days), clinical assessment included manual palpation to evaluate resting uterine tone, frequency & duration of contractions, fetal cardio tocography & ultrasound cervicometry to control the uterine, cervical changes at few hours & 48 hrs after treatment initiation, clinical evaluation of newborn was conducted according to generally accepted criteria

RESULTS

A cross sectional study, including 130 pregnant women distributed equally in the age group between 20-30 years and more than thirty in a proportion of 45.2%, with lower percent for those who were less than 20 years (9.2%) as shown in figure 1.

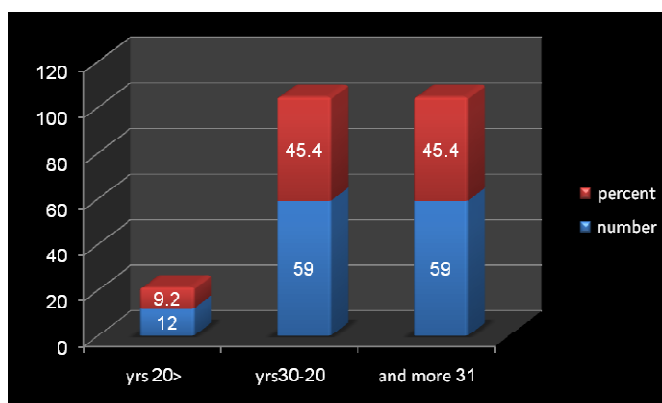


Figure 1: Distribution According to Age

Most of the pregnant women were from Al-Nasiriya city (76.2%) followed by Al-Shatra 13.8% And the Suq Al-Sheykh 10%

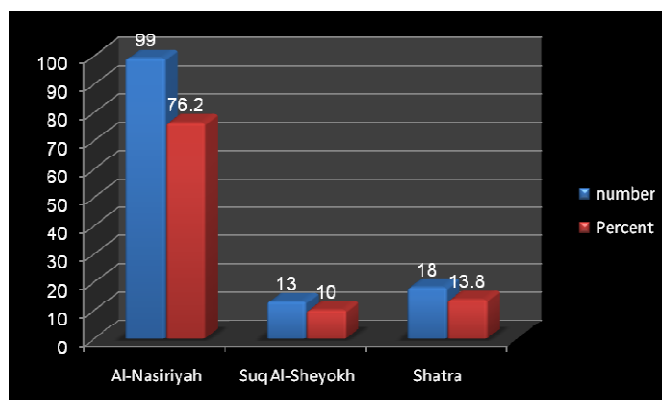
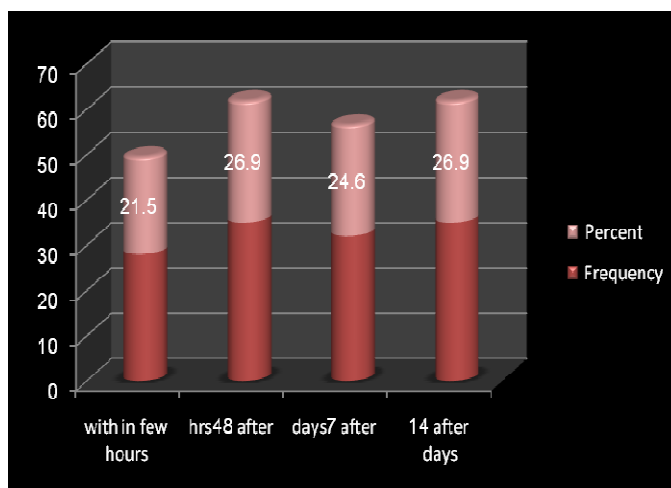


Figure 2: Distribution According to Residence

Table 1: Distribution According to the Main Personal Characters

Main Personal Characters	Status	Frequency	Percent
Chronic illness	None	114	87.7
	One or more	16	12.3
Parity	1-3	40	30.8
	4-6	77	59.2
	7 and more	13	10.0
Gravida	1-3	60	46.2
	4-6	44	33.8
	7 and more	26	20.0
Gestational age	24-27wks	34	26.2
	28-31wk	51	39.2
	32-34wk	45	34.6
Abortion history	None	66	50.8
	One time	35	26.9
	twice	19	14.6
	Three or more	10	7.7
Preterm labor	None	114	87.7
	One time	14	10.8
	twice	2	1.5
Total		130	100.0

Only 12.3% were with chronic medical illnesses, while majority of the studied population were with parity of 4-6 (59.2%), with gestational age 28-31wk (39.2%), negative history of abortion (50.8%) and (87.7%) negative history of preterm labor as shown in Table 1.

**Figure 3: Distribution According to the Time of Delivery****Table 2 A: Relationship between Treatment Strategies and Some Determinants**

			Treatment Strategy		Total	X ²
			Progesterone	Atosiban		P Value
Age by Years						
<div><20</div> <div>20-30</div> <div>>30</div>		No.	7	5	9.2	1.588
		%	58.3%	41.7%	%	.452
		No.	26	33	59	
		%	44.1%	55.9%	45.4%	
		No.	32	27	59	
		%	54.2%	45.8%	45.4%	

Table 2 A: Contd.,					
Address					
Al-Nasiriyah	No.	49	50	99	.925
	%	49.5%	50.5%	76%	0.630
Suq Al-Sheyokh	No.	8	5	13	
	%	61.5%	38.5%	10.0%	
Shatra	No.	8	10	18	
	%	44.4%	55.6%	14%	
Chronic illness					
No	No.	54	60	114	
	%	47.4%	52.6%	87.7%	2.875
Yes	No.	11	5	16	0.047
	%	69.2%	30.8%	12.3%	
Total	No.	65	65	130	
	%	50.0%	50.0%	100.0%	

There was no significant statistical association between the treatment strategies in form of Progesterone or atosiban with age, address and having medical illness or no, where P value >0.05 as shown in Table 2.

Also There was no significant statistical association between the treatment strategies in form of Progesterone or atosiban with number of CS and having CS or no, where P value >0.05 as shown in Figure 3

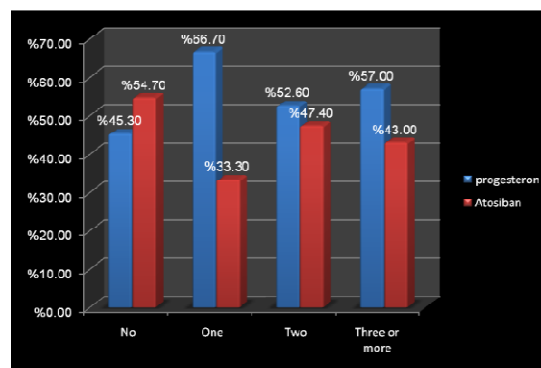


Figure 4: Association Between the Treatment Strategies with Number of Caesarean Section

Pearson Chi-Square= 2.997^a Significance=0.180^b

Table 2 B: Relationship Between treatment Strategies and Some Determinants

			Treatment		Total	X ²
			Progesteronee	Atosiban		P Value
Para	1-3	No.	23	17	40	1.613
		%	57.5%	42.5%	100.0%	0.446
	4-6	No.	35	42	77	
		%	45.5%	54.5%	100.0%	
	7 and more	No.	7	6	13	
		%	53.8%	46.2%	100.0%	
Gravida 1-3		No.	39	21	60	15.337
		%	65.0%	35.0%	100.0%	0.001
4-6		No.	21	23	44	
		%	47.7%	52.3%	100.0%	
7 and more 3.00		No.	5	21	26	
		%	19.2%	80.8%	100.0%	

Table 2 B: Contd.,					
Gestational age 24-27wks	No.	15	19	34	
	%	44.1%	55.9%	100.0%	1.736
28-31wk	No.	24	27	51	0.404
	%	47.1%	52.9%	100.0%	
32-34wk	No.	26	19	45	
	%	57.8%	42.2%	100.0%	
Abortion none	No.	27	39	66	5.475
	%	40.9%	59.1%	100.0%	0.045
One	No.	20	15	35	
	%	57.1%	42.9%	100.0%	
Two	No.	13	6	19	
	%	68.4%	31.6%	100.0%	
Three and more	No.	5	5	10	
	%	50.0%	50.0%	100.0%	
Preterm labor . none	No.	57	57	114	
	%	50.0%	50.0%	100.0%	2.286
One	No.	6	8	14	0.471
	%	42.9%	57.1%	100.0%	
Two	No.	2	0	2	
	%	100.0%	0.0%	100.0%	
Total	No.	65	65	130	
	%	50.0%	50.0%	100.0%	

There was a significant statistical association between the treatment strategies in form of Progesterone or atosiban with number of gravida and number of abortion, where P value <0.05 as shown in Table 2, while there was no significant statistical association between the treatment strategies in form of Progesterone or atosiban with parity gestational age and preterm labor, where P value >0.05 as shown in Table 2.

Table 3: Distribution of Outcome According to Treatment Strategies

			Treatment		Total	X ²
			Atosiban	Progesterone		P value
Delivery	within few hours	No.	8	20	28	17.092 0.0001
		%	28.6%	71.4%	100.0%	
	after 48 hrs	No.	12	23	35	
		%	34.3%	65.7%	100.0%	
	after 7 days	No.	20	12	32	
		%	62.5%	37.5%	100.0%	
	after 14 days	No.	25	10	35	
		%	71.4%	28.6%	100.0%	
Total		No.	65	65	130	
		%	50.0%	50.0%	100.0%	

There was a significant statistical association between the treatment strategies in form of Progesterone or atosiban with outcome of delivery, where P value <0.05 as shown in Table 3.

Table 4: Effect of Type of Treatment on the Time of Delivery According to Gestational Age

Treatment				Time of Delivery				Total	X ² , P Value
				Within Few Hours	After 48 Hrs	After 1 Week	After 14 Days		F.E, P Value
Atosiban	Gestational age	24-27wks	No.	3	2	4	6	15	2.171
			%	20.0%	13.3%	26.7%	40.0%	100.0%	0.903
		28-31wk	No.	2	5	9	8	24	
			%	8.3%	20.8%	37.5%	33.3%	100.0%	
		32-34wk	No.	3	5	7	11	26	
			%	11.5%	19.2%	26.9%	42.3%	100.0%	
		Total	No.	8	12	20	25	65	
			%	12.3%	18.5%	30.8%	38.5%	100.0%	
Progeste-rone	Gestational age	24-27wks	No.	9	6	3	1	19	4.880
			%	47.4%	31.6%	15.8%	5.3%	100.0%	0.048
		28-31wk	No.	7	9	6	5	27	
			%	25.9%	33.3%	22.2%	18.5%	100.0%	
		32-34wk	No.	4	8	3	4	19	
			%	21.1%	42.1%	15.8%	21.1%	100.0%	
		Total	No.	20	23	12	10	65	
			%	30.8%	35.4%	18.5%	15.4%	100.0%	

Table 5: Effect of Type of Treatment on the Time of Delivery According to History of Preterm Labor

Treatment				Delivery				Total	
				Within Few Hours	After 48 Hrs	After 7 Days	After 14 Days		
Atosiban	Preterm labor	None	No.	8	12	18	19	57	7.047
			%	14.0%	21.1%	31.6%	33.3%	100.0%	.286
		One	No.	0	0	1	5	6	
			%	0.0%	0.0%	16.7%	83.3%	100.0%	
		Two	No.	0	0	1	1	2	
			%	0.0%	0.0%	50.0%	50.0%	100.0%	
		Total	No.	8	12	20	25	65	
			%	12.3%	18.5%	30.8%	38.5%	100.0%	
Progeste-rone	Preterm labor	None	No.	18	19	11	9	57	.859
			%	31.6%	33.3%	19.3%	15.8%	100.0%	.909
		One	No.	2	4	1	1	8	
			%	25.0%	50.0%	12.5%	12.5%	100.0%	
		Total	No.	20	23	12	10	65	
			%	30.8%	35.4%	18.5%	15.4%	100.0%	

There was no significant statistical association between the treatment strategies in form of both with preterm labor according to the clinical outcome of delivery, where P value <0.05 as shown in Table 5

DISCUSSIONS

Across sectional study including 130 pregnant women distributed equally at the age group between 20-40 yrs. There are 87.7% of pregnant women without history of chronic illness, 12.3% with history of chronic illness like hypertension, diabetes mellitus or bronchial asthma. Majority of the studied women were with parity of 4-6 (59.2%) while (30.8%) with parity 1-3, the main gestational age was 28-31 wks (39%), 24-27 wks (26.2%) & 32-34 wks (34.6%). Negative history of abortion 50.8%, Negative history of preterm labor 87.7% as shown in table 1.

Majority of cases with negative history of caesarean section (60.2%) while those with 1 or 2 caesarean section were nearly equal distribution.

There was no significant statistical association between the treatment strategies in form of atosiban or progesterone with age, address & having medical illness or no where p value > 0.05 as shown in Table 2. There was no significant statistical association between the treatment strategies in form of atosiban or progesterone with parity, gestational age & preterm labor where P value > 0.05 as shown in table 2, while there was significant statistical association between the treatment strategies in form of atosiban or progesterone with outcome of delivery where P value > 0.05 as shown in Table 3

In atosiban group (65) pregnant women, there were 12 women (34.3%) deliver after 48 hrs, 20 women (62.5%) deliver after 7 days while 25 women (71.4%) deliver after 14 days . It should be noted that 20 women in atosiban group underwent a second complete treatment course.

Tocolysis failed in 8 pregnant women (28.6%) receiving atosiban & delivered within few hours, in progesterone group there were 23 (65.7%) delivered after 48 hrs 12 (37.5%) deliver after 7 days & 10 (28.6%) deliver after 14 days, tocolysis failed in 20 (71.4%) pregnant women receiving progesterone & delivered within few hours.

After the diagnosis of threatened preterm labor all pregnant women received dexamethasone in a course dose of 24 mg to prevent fetal respiratory distress syndrome & underwent tocolytic therapy by the same above dosage regimes.

The atosiban was more effective & good outcomes in prolongation of pregnancy & prevent preterm labor in comparison with progesterone.

Full term birth occurred in 20 of the cases in atosiban group (62.5%) while only 8 in progesterone group (28.6%), no significant differences in the body weight of newborns were observed in the studied groups. First minute Apgar score ranged from 5-8 & did not differ significantly between the two groups.

Atosiban showed a favorable safety profile, the tocolytic effect of atosiban occurred significantly earlier effective mechanism that triggers & supports uterine contraction activity, at the same time duration of pregnancy prolongation after tocolysis was significantly longer in the atosiban group.

Studies in Russian federation, Moscow compared the effectiveness & safety of atosiban & nifedipine in pregnant women with threatened preterm labor ⁽¹⁴⁾, they were found that the effectiveness of nifedipine & atosiban in pregnancy prolongation for 48 hrs in threatened preterm labor is comparable.

CONCLUSIONS

The atosiban more effective in management & prolongation for more than 48 hrs in threatened preterm labor in comparison with progesterone, there for postponing delivery for 48 hrs in order to allow maximal effect of maternal parenteral steroid administration & trans portion of the pregnant women to a centre with neonatal intensive care unit.

RECOMMENDATIONS

- Encourage hospital delivery for all preterm labor.
- Further studies are needed to clarify the effectiveness & safety of these drugs in management of the threatened labor in multiple pregnancies.

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